



SEQUENCE LISTING

<110> Gravel, Roy A,
Rozen, Rima
Leclerc, Daniel
Wilson, Aaron
Rosenblatt, David

<120> HUMAN METHIONINE SYNTHASE REDUCTASE:
CLONING, AND METHODS FOR EVALUATING RISK OF NEURAL TUBE
DEFECTS, CARDIOVASCULAR DISEASE, CANCER, AND DOWN'S SYNDROME

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<150> 09/371,347
<151> 1999-08-10

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<151> 1999-01-15

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<151> 1998-01-16

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Glu Thr Ala Pro Leu Val Val Val Ser Thr Thr Gly Thr Gly Asp
50 55 60
Pro Pro Asp Thr Ala Arg Lys Phe Val Lys Glu Ile Gln Asn Gln Thr
65 70 75 80
Leu Pro Val Asp Phe Phe Ala His Leu Arg Tyr Gly Leu Leu Gly Leu
85 90 95
Gly Asp Ser Glu Tyr Thr Tyr Phe Cys Asn Gly Gly Lys Ile Ile Asp
100 105 110
Lys Arg Leu Gln Glu Leu Gly Ala Arg His Phe Tyr Asp Thr Gly His
115 120 125
Ala Asp Asp Cys Val Gly Leu Glu Leu Val Val Glu Pro Trp Ile Ala
130 135 140
Gly Leu Trp Pro Ala Leu Arg Lys His Phe Arg Ser Ser Arg Gly Gln
145 150 155 160
Glu Glu Ile Ser Gly Ala Leu Pro Val Ala Ser Pro Ala Ser Leu Arg
165 170 175
Thr Asp Leu Val Lys Ser Glu Leu Leu His Ile Glu Ser Gln Val Glu
180 185 190
Leu Leu Arg Phe Asp Asp Ser Gly Arg Lys Asp Ser Glu Val Leu Lys
195 200 205
Gln Asn Ala Val Asn Ser Asn Gln Ser Asn Val Val Ile Glu Asp Phe
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Glu Ser Ser Leu Thr Arg Ser Val Pro Pro Leu Ser Gln Ala Ser Leu
225 230 235 240
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Ser Leu Gly Gln Glu Glu Ser Gln Val Ser Val Thr Ser Ala Asp Pro
260 265 270

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 275 280 285
 Ala Ile Lys Thr Thr Leu Leu Val Glu Leu Asp Ile Ser Asn Thr Asp
 290 295 300
 Phe Ser Tyr Gln Pro Gly Asp Ala Phe Ser Val Ile Cys Pro Asn Ser
 305 310 315 320
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 325 330 335
 Arg Glu His Cys Val Leu Leu Lys Ile Lys Ala Asp Thr Lys Lys Lys
 340 345 350
 Gly Ala Thr Leu Pro Gln His Ile Pro Ala Gly Cys Ser Leu Gln Phe
 355 360 365
 Ile Phe Thr Trp Cys Leu Glu Ile Arg Ala Ile Pro Lys Lys Ala Phe
 370 375 380
 Leu Arg Ala Leu Val Asp Tyr Thr Ser Asp Ser Ala Glu Lys Arg Arg
 385 390 395 400
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 405 410 415
 Val Arg Asp Ala Cys Ala Cys Leu Leu Asp Leu Leu Leu Ala Phe Pro
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 Ser Cys Gln Pro Pro Leu Ser Leu Leu Glu His Leu Pro Lys Leu
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 Gln Pro Arg Pro Tyr Ser Cys Ala Ser Ser Ser Leu Phe His Pro Gly
 450 455 460
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 465 470 475 480
 Thr Glu Val Leu Arg Lys Gly Val Cys Thr Gly Trp Leu Ala Leu Leu
 485 490 495
 Val Ala Ser Val Leu Gln Pro Asn Ile His Ala Ser His Glu Asp Ser
 500 505 510
 Gly Lys Ala Leu Ala Pro Lys Ile Ser Ile Ser Pro Arg Thr Thr Asn
 515 520 525
 Ser Phe His Leu Pro Asp Asp Pro Ser Ile Pro Ile Ile Met Val Gly
 530 535 540
 Pro Gly Thr Gly Ile Ala Pro Phe Ile Gly Phe Leu Gln His Arg Glu
 545 550 555 560
 Lys Leu Gln Glu Gln His Pro Asp Gly Asn Phe Gly Ala Met Trp Leu
 565 570 575
 Phe Phe Gly Cys Arg His Lys Asp Arg Asp Tyr Leu Phe Arg Lys Glu
 580 585 590
 Leu Arg His Phe Leu Lys His Gly Ile Leu Thr His Leu Lys Val Ser
 595 600 605
 Phe Ser Arg Asp Ala Pro Val Gly Glu Glu Ala Pro Ala Lys Tyr
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 Val Gln Asp Asn Ile Gln Leu His Gly Gln Gln Val Ala Arg Ile Leu
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 645 650 655
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Pro Pro Asp Thr Ala Arg Lys Phe Val Lys Glu Ile Gln Asn Gln Thr		
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Leu Pro Val Asp Phe Phe Ala His Leu Arg Tyr Gly Leu Leu Gly Leu		
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Gly Asp Ser Glu Tyr Thr Tyr Phe Cys Asn Gly Gly Lys Ile Ile Asp		
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Lys Arg Leu Gln Glu Leu Gly Ala Arg His Phe Tyr Asp Thr Gly His		
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Ala Asp Asp Cys Val Gly Leu Glu Leu Val Val Glu Pro Trp Ile Ala		
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Gly Leu Trp Pro Ala Leu Arg Lys His Phe Arg Ser Ser Arg Gly Gln		
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Thr Asp Leu Val Lys Ser Glu Leu Leu His Ile Glu Ser Gln Val Glu
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 Val Phe Gln Val Pro Ile Ser Lys Ala Val Gln Leu Thr Thr Asn Asp
 275 280 285
 Ala Ile Lys Thr Thr Leu Leu Val Glu Leu Asp Ile Ser Asn Thr Asp
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 Phe Ser Tyr Gln Pro Gly Asp Ala Phe Ser Val Ile Cys Pro Asn Ser
 305 310 315 320
 Asp Ser Glu Val Gln Ser Leu Leu Gln Arg Leu Gln Leu Glu Asp Lys
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 Arg Glu His Cys Val Leu Leu Lys Ile Lys Ala Asp Thr Lys Lys Lys
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 Gly Ala Thr Leu Pro Gln His Ile Pro Ala Gly Cys Ser Leu Gln Phe
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 420 425 430
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 Gln Pro Arg Pro Tyr Ser Cys Ala Ser Ser Ser Leu Phe His Pro Gly
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 465 470 475 480
 Thr Glu Val Leu Arg Lys Gly Val Cys Thr Gly Trp Leu Ala Leu Leu
 485 490 495
 Val Ala Ser Val Leu Gln Pro Asn Ile His Ala Ser His Glu Asp Ser
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 Gly Lys Ala Leu Ala Pro Lys Ile Ser Ile Ser Pro Arg Thr Thr Asn
 515 520 525
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 530 535 540
 Pro Gly Thr Gly Ile Ala Pro Phe Ile Gly Phe Leu Gln His Arg Glu
 545 550 555 560
 Lys Leu Gln Glu Gln His Pro Asp Gly Asn Phe Gly Ala Met Trp Leu
 565 570 575
 Phe Phe Gly Cys Arg His Lys Asp Arg Asp Tyr Leu Phe Arg Lys Glu
 580 585 590
 Leu Arg His Phe Leu Lys His Gly Ile Leu Thr His Leu Lys Val Ser
 595 600 605
 Phe Ser Arg Asp Ala Pro Val Gly Glu Glu Glu Ala Pro Ala Lys Tyr
 610 615 620
 Val Gln Asp Asn Ile Gln Leu His Gly Gln Gln Val Ala Arg Ile Leu

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Leu Gln Glu Asn Gly His Ile Tyr Val Cys Gly Asp Ala Lys Asn Met			
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Ala Lys Asp Val His Asp Ala Leu Val Gln Ile Ile Ser Lys Glu Val			
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Gly Val Glu Lys Leu Glu Ala Met Lys Thr Leu Ala Thr Leu Lys Glu			
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Glu Glu Lys Leu Cys Ala Ile Val Val Ser Ser Thr Gly Asp Gly Asp			
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Ala Pro Asp Asn Cys Ala Arg Phe Val Arg Arg Ile Asn Arg Asn Ser			
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Leu Glu Asn Glu Tyr Leu Lys Asn Leu Asp Tyr Val Leu Leu Gly Leu			
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Gly Asp Ser Asn Tyr Ser Ser Tyr Gln Thr Ile Pro Arg Lys Ile Asp			
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Gln Thr Leu Ser Asn Asp Glu Asn Leu Arg Val Pro Ile Ala Pro Gln			
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Pro Phe Ile Val Ser Ser Val Ser Asn Arg Lys Leu Pro Glu Asp Thr			
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Lys Leu Glu Trp Gln Asn Leu Cys Lys Met Pro Gly Val Val Thr Lys			
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Pro Phe Glu Val Leu Val Val Ser Ala Glu Phe Val Thr Asp Pro Phe			
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 Val Leu Asp Ile Ala Asp Gln Gln Cys Glu Leu Ser Ile Asn Pro Lys
 340 345 350
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 355 360 365
 Thr Leu Arg His Met Phe Thr Thr Cys Leu Asp Ile Arg Arg Ala Pro
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 385 390 395 400
 Glu Lys Arg Arg Leu Leu Glu Leu Cys Ser Ala Gln Gly Met Lys Asp
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 580 585 590
 Leu Thr Asp Leu Ile Ile Cys Glu Ser Glu Gln Lys Gly Glu Arg Val
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 Gln Asp Gly Leu Arg Lys Tyr Leu Asp Lys Val Leu Pro Phe Leu Thr
 610 615 620
 Ala Ser Thr Glu Ser Lys Ile Phe Ile Cys Gly Asp Ala Lys Gly Met
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 Ser Lys Asp Val Trp Gln Cys Phe Ser Asp Ile Val Ala Ser Asp Gln
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Arg Glu Ser Ser Phe Val Glu Lys Met Lys Lys Thr Gly Arg Asn Ile		
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Ile Val Phe Tyr Gly Ser Gln Thr Gly Thr Ala Glu Glu Phe Ala Asn		
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Arg Leu Ser Lys Asp Ala His Arg Tyr Gly Met Arg Gly Met Ser Ala		
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Asp Pro Glu Glu Tyr Asp Leu Ala Asp Leu Ser Ser Leu Pro Glu Ile		
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Asp Asn Ala Leu Val Val Phe Cys Met Ala Thr Tyr Gly Glu Gly Asp		
130	135	140
Pro Thr Asp Asn Ala Gln Asp Phe Tyr Asp Trp Leu Gln Glu Thr Asp		
145	150	155
Val Asp Leu Ser Gly Val Lys Phe Ala Val Phe Gly Leu Gly Asn Lys		
165	170	175
Thr Tyr Glu His Phe Asn Ala Met Gly Lys Tyr Val Asp Lys Arg Leu		
180	185	190
Glu Gln Leu Gly Ala Gln Arg Ile Phe Glu Leu Gly Leu Gly Asp Asp		
195	200	205
Asp Gly Asn Leu Glu Glu Asp Phe Ile Thr Trp Arg Glu Gln Phe Trp		
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Pro Ala Val Cys Glu His Phe Gly Val Glu Ala Thr Gly Glu Glu Ser		
225	230	235
Ser Ile Arg Gln Tyr Glu Leu Val Val His Thr Asp Ile Asp Ala Ala		
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Lys Val Tyr Met Gly Glu Met Gly Arg Leu Lys Ser Tyr Glu Asn Gln		
260	265	270
Lys Pro Pro Phe Asp Ala Lys Asn Pro Phe Leu Ala Ala Val Thr Thr		
275	280	285
Asn Arg Lys Leu Asn Gln Gly Thr Glu Arg His Leu Met His Leu Glu		
290	295	300
Leu Asp Ile Ser Asp Ser Lys Ile Arg Tyr Glu Ser Gly Asp His Val		
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Ala Val Tyr Pro Ala Asn Asp Ser Ala Leu Val Asn Gln Leu Gly Lys		
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Ile Leu Gly Ala Asp Leu Asp Val Val Met Ser Leu Asn Asn Leu Asp		
340	345	350
Glu Glu Ser Asn Lys Lys His Pro Phe Pro Cys Pro Thr Ser Tyr Arg		
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Thr Ala Leu Thr Tyr Tyr Leu Asp Ile Thr Asn Pro Pro Arg Thr Asn		
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Val Leu Tyr Glu Leu Ala Gln Tyr Ala Ser Glu Pro Ser Glu Gln Glu		
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Leu Leu Arg Lys Met Ala Ser Ser Ser Gly Glu Gly Lys Glu Leu Tyr		
405	410	415
Leu Ser Trp Val Val Glu Ala Arg Arg His Ile Leu Ala Ile Leu Gln		
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Asp Cys Pro Ser Leu Arg Pro Pro Ile Asp His Leu Cys Glu Leu Leu		
435	440	445
Pro Arg Leu Gln Ala Arg Tyr Tyr Ser Ile Ala Ser Ser Ser Lys Val		
450	455	460
His Pro Asn Ser Val His Ile Cys Ala Val Val Val Glu Tyr Glu Thr		
465	470	475
		480

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 Lys Glu Pro Val Gly Glu Asn Gly Gly Arg Ala Leu Val Pro Met Phe
 500 505 510
 Val Arg Lys Ser Gln Phe Arg Leu Pro Phe Lys Ala Thr Thr Pro Val
 515 520 525
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 Val Ala Phe Ser Arg Glu Gln Ser His Lys Val Tyr Val Gln His Leu
 595 600 605
 Leu Lys Gln Asp Arg Glu His Leu Trp Lys Leu Ile Glu Gly Gly Ala
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 His Ile Tyr Val Cys Gly Asp Ala Arg Asn Met Ala Arg Asp Val Gln
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 Asn Thr Phe Tyr Asp Ile Val Ala Glu Leu Gly Ala Met Glu His Ala
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 taggtcaagc agaggacaag aggagataag tggcgcactc ccgggtggcat cacctgcac 600
 cttgaggaca gaccttggta agtcagagct gctacacatt gaatctcaag tcgagcttct 660
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<213> *Saccharomyces cerevisiae*

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<210> 38
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<213> *Thiocapsa roseopersicina*

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<210> 39
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<213> *Pisum sativum*

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<210> 40
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<213> *Spinacia oleracea*

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<212> DNA

<213> Homo sapiens

<400> 41

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<210> 42

<211> 698

<212> PRT

<213> Homo sapiens

<400> 42

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 Lys Arg Leu Gln Glu Leu Gly Ala Arg His Phe Tyr Asp Thr Gly His
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 Ala Asp Asp Cys Val Gly Leu Glu Leu Val Val Glu Pro Trp Ile Ala
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 Gly Leu Trp Pro Ala Leu Arg Lys His Phe Arg Ser Ser Arg Gly Gln
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 Glu Glu Ile Ser Gly Ala Leu Pro Val Ala Ser Pro Ala Ser Leu Arg
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 Thr Asp Leu Val Lys Ser Glu Leu Leu His Ile Glu Ser Gln Val Glu
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 Leu Leu Arg Phe Asp Asp Ser Gly Arg Lys Asp Ser Glu Val Leu Lys
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 Gln Asn Ala Val Asn Ser Asn Gln Ser Asn Val Val Ile Glu Asp Phe
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 Val Phe Gln Val Pro Ile Ser Lys Ala Val Gln Leu Thr Thr Asn Asp
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 Ala Ile Lys Thr Thr Leu Leu Val Glu Leu Asp Ile Ser Asn Thr Asp
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 Val Arg Asp Ala Cys Ala Cys Leu Leu Asp Leu Leu Leu Ala Phe Pro
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 Gln Pro Arg Pro Tyr Ser Cys Ala Ser Ser Ser Leu Phe His Pro Gly
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 Val Ala Ser Val Leu Gln Pro Asn Ile His Ala Ser His Glu Asp Ser
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 Gly Lys Ala Leu Ala Pro Lys Ile Ser Ile Ser Pro Arg Thr Thr Asn
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 Ser Phe His Leu Pro Asp Asp Pro Ser Ile Pro Ile Ile Met Val Gly
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 Pro Gly Thr Gly Ile Ala Pro Phe Ile Gly Phe Leu Gln His Arg Glu

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Leu Arg His Phe Leu Lys His Gly Ile Leu Thr His Leu Lys Val Ser			
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Phe Ser Arg Asp Ala Pro Val Gly Glu Glu Ala Pro Ala Lys Tyr			
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Val Gln Asp Asn Ile Gln Leu His Gly Gln Gln Val Ala Arg Ile Leu			
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Leu Gln Glu Asn Gly His Ile Tyr Val Cys Gly Asp Ala Lys Asn Met			
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Ala Lys Asp Val His Asp Ala Leu Val Gln Ile Ile Ser Lys Glu Val			
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<212> DNA
<213> Homo sapiens

<400> 43

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<212> PRT
<213> Homo sapiens

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Glu Thr Ala Pro Leu Val Val Val Ser Thr Thr Gly Thr Gly Asp
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Pro Pro Asp Thr Ala Arg Lys Phe Val Lys Glu Ile Gln Asn Gln Thr
65 70 75 80
Leu Pro Val Asp Phe Phe Ala His Leu Arg Tyr Gly Leu Leu Gly Leu
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Gly Asp Ser Glu Tyr Thr Phe Cys Asn Gly Gly Lys Ile Ile Asp
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Lys Arg Leu Gln Glu Leu Gly Ala Arg His Phe Tyr Asp Thr Gly His
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Ala Asp Asp Cys Val Gly Leu Glu Leu Val Val Glu Pro Trp Ile Ala
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145 150 155 160
Glu Glu Ile Ser Gly Ala Leu Pro Val Ala Ser Pro Ala Ser Leu Arg
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Val Arg Asp Ala Cys Ala Cys Leu Leu Asp Leu Leu Leu Ala Phe Pro		
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<211> 697

<212> PRT

<213> Homo sapiens

<400> 46

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Ala	Asp	Leu	His	Cys	Ile	Ser	Glu	Ser	Asp	Lys	Tyr	Asp	Leu	Lys	Thr
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Glu	Thr	Ala	Pro	Leu	Val	Val	Val	Val	Ser	Thr	Thr	Gly	Thr	Gly	Asp
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Pro	Pro	Asp	Thr	Ala	Arg	Lys	Phe	Val	Lys	Glu	Ile	Gln	Asn	Gln	Thr
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Gly	Asp	Ser	Glu	Tyr	Thr	Tyr	Phe	Cys	Asn	Gly	Gly	Lys	Ile	Ile	Asp
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Lys	Arg	Leu	Gln	Glu	Leu	Gly	Ala	Arg	His	Phe	Tyr	Asp	Thr	Gly	His
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Gly	Leu	Trp	Pro	Ala	Leu	Arg	Lys	His	Phe	Arg	Ser	Ser	Arg	Gly	Gln
145								150			155			160	
Glu	Glu	Ile	Ser	Gly	Ala	Leu	Pro	Val	Ala	Ser	Pro	Ala	Ser	Leu	Arg

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Asn Ile Pro Gly Leu Pro Pro Glu Tyr Leu Gln Val His Leu Gln Glu			
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Val Phe Gln Val Pro Ile Ser Lys Ala Val Gln Leu Thr Thr Asn Asp			
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Asp Ser Glu Val Gln Ser Leu Leu Gln Arg Leu Gln Leu Glu Asp Lys			
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355	360	365	
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385	390	395	400
Leu Gln Glu Leu Cys Ser Lys Gln Gly Ala Ala Asp Tyr Ser Arg Phe			
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Val Arg Asp Ala Cys Ala Cys Leu Leu Asp Leu Leu Leu Ala Phe Pro			
420	425	430	
Ser Cys Gln Pro Pro Leu Ser Leu Leu Leu Glu His Leu Pro Lys Leu			
435	440	445	
Gln Pro Arg Pro Tyr Ser Cys Ala Ser Ser Ser Leu Phe His Pro Gly			
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Lys Leu His Phe Val Phe Asn Ile Val Glu Phe Leu Ser Thr Ala Thr			
465	470	475	480
Thr Glu Val Leu Arg Lys Gly Val Cys Thr Gly Trp Leu Ala Leu Leu			
485	490	495	
Val Ala Ser Val Leu Gln Pro Asn Ile His Ala Ser His Glu Asp Ser			
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Gly Lys Ala Leu Ala Pro Lys Ile Ser Ile Ser Pro Arg Thr Thr Asn			
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Ser Phe His Leu Pro Asp Asp Pro Ser Ile Pro Ile Ile Met Val Gly			
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Pro Gly Thr Gly Ile Ala Pro Phe Ile Gly Phe Leu Gln His Arg Glu			
545	550	555	560
Lys Leu Gln Glu Gln His Pro Asp Gly Asn Phe Gly Ala Met Trp Phe			
565	570	575	
Phe Gly Cys Arg His Lys Asp Arg Asp Tyr Leu Phe Arg Lys Glu Leu			
580	585	590	
Arg His Phe Leu Lys His Gly Ile Leu Thr His Leu Lys Val Ser Phe			
595	600	605	
Ser Arg Asp Ala Pro Val Gly Glu Glu Ala Pro Ala Lys Tyr Val			
610	615	620	

Gln	Asp	Asn	Ile	Gln	Leu	His	Gly	Gln	Gln	Val	Ala	Arg	Ile	Leu	Leu
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Lys	Asp	Val	His	Asp	Ala	Leu	Val	Gln	Ile	Ile	Ser	Lys	Glu	Val	Gly
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Val	Glu	Lys	Leu	Glu	Ala	Met	Lys	Thr	Leu	Ala	Thr	Leu	Lys	Glu	Glu
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<211> 2093
<212> DNA
<213> Homo sapiens

<400> 47

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<211> 689
<212> PRT

<213> Homo sapiens

<400> 48

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35 40 45
Thr Ala Pro Leu Val Val Val Ser Thr Thr Gly Thr Gly Asp Pro
50 55 60
Pro Asp Thr Ala Arg Lys Phe Val Lys Glu Ile Gln Asn Gln Thr Leu
65 70 75 80
Pro Val Asp Phe Phe Ala His Leu Arg Tyr Gly Leu Leu Gly Leu Gly
85 90 95
Asp Ser Glu Tyr Thr Tyr Phe Cys Asn Gly Gly Lys Ile Ile Asp Lys
100 105 110
Arg Leu Gln Glu Leu Gly Ala Arg His Phe Tyr Asp Thr Gly His Ala
115 120 125
Asp Asp Cys Val Gly Leu Glu Leu Val Val Glu Pro Trp Ile Ala Gly
130 135 140
Leu Trp Pro Ala Leu Arg Lys His Phe Arg Ser Ser Arg Gly Gln Glu
145 150 155 160
Glu Ile Ser Gly Ala Leu Pro Val Ala Ser Pro Ala Ser Leu Arg Thr
165 170 175
Asp Leu Val Lys Ser Glu Leu Leu His Ile Glu Ser Gln Val Glu Leu
180 185 190
Leu Arg Phe Asp Asp Ser Gly Arg Lys Asp Ser Glu Val Leu Lys Gln
195 200 205
Asn Ala Val Asn Ser Asn Gln Ser Asn Val Val Ile Glu Asp Phe Glu
210 215 220
Ser Ser Leu Thr Arg Ser Val Pro Pro Leu Ser Gln Ala Ser Leu Asn
225 230 235 240
Ile Pro Gly Leu Pro Pro Glu Tyr Leu Gln Val His Leu Gln Glu Ser
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260 265 270
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275 280 285
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Glu His Cys Val Leu Leu Lys Ile Lys Ala Asp Thr Lys Lys Lys Gly
340 345 350
Ala Thr Leu Pro Gln His Ile Pro Ala Gly Cys Ser Leu Gln Phe Ile
355 360 365
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385 390 395 400
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405 410 415
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 Lys Ala Leu Ala Pro Lys Ile Ser Ile Ser Pro Arg Thr Thr Asn Ser
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 595 600 605
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 <213> Homo sapiens

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23

<210> 50
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26

<210> 51
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<400> 51

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<213> Homo sapiens

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<211> 23
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<210> 56
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<210> 57
<211> 17
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<210> 58
<211> 22
<212> PRT
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<211> 6
<212> PRT
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<400> 60
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<212> DNA
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<210> 62
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<400> 62
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<210> 63
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